REMARKS

Amendments to the Claims

Claims 1, 6-10, 12-16, 22, 28, 32-60 are currently pending and stand rejected. Claim 61 is withdrawn. Claims 6, 8, 16, 22, 34, 37 and 41-42 are amended, claims 1, 7, 12-15, 28, 35-36, 38-40, 43-44 and 61 are cancelled without prejudice or disclaimer, and claims 62 and 63 are added herein. Claims 6, 8, 16, 22, 34, 37 and 41-42 are amended to update dependency and are supported throughout the specification and claims as originally filed.

Claims 6, 8-10, 16, 22, 32-34, 37, 41, 45-60 and 62-63 will be pending and under consideration after entry of the present amendment. No new matter is added.

Restriction Requirement

The Applicants note that claim 61 is withdrawn from further consideration in this application pursuant to 37 C.F.R. § 1.142(b) as drawn to a nonelected species. Claim 61 is cancelled herein without prejudice or disclaimer and the Applicants reserve the right to file a divisional application directed to the subject matter of this claim during the pendency of the present application.

Withdrawn Rejections

The Applicants respectfully note the withdrawal of the following rejections:

- the rejection of claims 1, 6-16, 22, 28, 32-44, 50-51 and 57-58 under 35 U.S.C. § 112, second paragraph; and
- the rejection of claims 45-48, 50-55 and 57-60 under 35 U.S.C. § 102(b) as anticipated by WO 98/04281 "because the amended claims now require that the

antibody is administered only via the intravenous route wherein this is not disclosed in WO 98/04281."

Correction of Inventorship Under 37 C.F.R. § 1.48(b)

Please delete Timothy A. Stewart and Mark D. Pescovitz as inventors in the present application. The invention of each of these inventors is no longer being claimed in the present application. The correct inventors of the amended application are: Antonio J. Grillo-Lopez and Lori A Kunkel.

The Commissioner is hereby authorized to charge Deposit Account No. 18-1260 in the amount of $130.00 to cover the processing fee as set forth in 37 C.F.R. § 1.17(i).

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1, 6-16, 22, 28 and 32-60 stand rejected under 35 U.S.C. § 112, first paragraph as lacking sufficient descriptive support. In particular, the Examiner asserts that the claim phrase "wherein after a first intravenous administration of said antibody the circulating levels of B cells in the human are reduced to block said immune response" of claims 1 and 28 is not supported in the specification. Applicants respectfully disagree with this assertion, and reserve the right to rebut it, should it be presented as an issue in the future. However, in as claims 1 and 28 are cancelled herein and no other pending claims recite this phrase, this basis of rejection is rendered moot and withdrawal is respectfully requested.

The Examiner also asserts that the claim phrase "wherein each administration of the antibody is by intravenous injection" of claims 45 and 46 is not supported in the specification.

The Examiner submits that the specification "does not disclose use of intravenous administration to the exclusion of other administration routes." In response, the Applicants respectfully direct the Examiner's attention, for example, to Example 3 of the specification (page 46, line 25 to page 47, line 25). This example describes a treatment regimen using periodic infusions of RITUXAN®. RITUXAN® is an anti-CD20 antibody composition formulated for intravenous administration. *See* RITUXAN® product insert (enclosed). As such, the infusion protocol described in Example 3 is a literal description of an exclusively intravenous administration protocol. Similarly, the Applicants direct the Examiner's attention to original claim 11. This claim specified intravenous administration of an anti-CD20 antagonist for blocking an immune response to a foreign antigen.

Applicants also note that this situation is a typical one where an applicant is electing to claim less than what is literally described in the disclosure. The written description plainly describes protocols for administration that include intravenous injections, but also describes situations where administration of the anti-CD20 antibodies of the present invention may occur through different means. The election of the Applicants to not seek claims commensurate with the full range of options for administration described in the specification cannot be fairly portrayed by the Examiner as an issue of compliance with written description. Moreover, there is no suggestion by the Examiner that an exclusively intravenous route of administration will not work; to the contrary, Applicants have provided literature demonstrating that this intravenous administrations of rituximab have proven effective in preventing allogeneic graft rejections and host-versus-graft rejections.

Accordingly, the Applicants respectfully submit that it would have been clear to one of skill it the art that the claimed administration of the anti-CD20 antibody by intravenous injection was supported by the specification as originally filed. Withdrawal of this rejection is therefore respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 6, 12-16, 22, 28, 34-39 and 43-44 stand rejected under 35 U.S.C. § 102(b) as anticipated by WO 98/04281 ("Davis et al.") for reasons set forth in the Office Action mailed July 28, 2004. In addition, the Examiner noted that the Applicants' observations regarding the determinations of the USPTO that certain claims of U.S. Application No. 09/905,836 ("the '836 application") lack enablement and sufficient written description were "not germane the invention under consideration." The Examiner maintains that Davis et al. and the present application provide equivalent disclosures regarding the currently claimed methods.

The Applicants submit that the proposed combination of references fails to render the present claims obvious for at least the reasons of record. However, claims 1, 12-15, 28, 35-36, 38-39 and 43-44 are cancelled herein, thus rendering this rejection moot as it applied to these claims. Claims 6, 16, 22, 34 and 37 are amended herein to depend from claims 45 or 46, which are limited to intravenous administration of an anti-CD20 antibody. Such administration has been noted by the Examiner as not disclosed in Davis et al. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 103(a)

1. **Davis et al. in view of Business Wire (2/24/1998)**

Claims 1, 6-10, 12-16, 22, 28, 32, 34-41 and 43-44 stand rejected under 35 U.S.C. § 103(a) as obvious over Davis et al., viewed in light of Business Wire (2/24/1998) for reasons set forth in the Office Action mailed July 28, 2004. In the present action the Examiner explains that the motivation for combining these references is that "IDEC-Y2B8 exhibits excellent in vivo retention of yttrium." Office Action, page 8.

The Applicants submit that the proposed combination of references fails to render the present claims obvious for at least the reasons of record. However, claims 1, 7, 12-15, 28, 35-36, 38-40 and 43-44 are cancelled herein, thus rendering this rejection moot as it applied to these claims. Amended claims 6, 8-10, 16, 22, 32, 34, 37 and 41 now depend from claims 45 or 46, which are limited to intravenous administration of an anti-CD20 antibody. Such administration has been noted by the Examiner as not disclosed in Davis et al. Accordingly, the Applicants respectfully request withdrawal of this rejection.

2. **Davis et al. in view of U.S. Patent No. 6,498,181**

Claims 1, 6-10, 12-16, 22, 28, 33, 34-39 and 42-44 stand rejected under 35 U.S.C. § 103(a) as obvious over Davis et al., viewed in light of U.S. Patent No. 6,498,181 ("Gehlsen") for reasons set forth in the Office Action mailed July 28, 2004.

The Applicants submit that the proposed combination of references fails to render the present claims obvious for at least the reasons of record. However, claims 1, 7, 12-15, 28, 35-36, 38-39 and 42-44 are cancelled herein, thus rendering this rejection moot as it applied to these claims. Amended claims 6, 8-10, 16, 22, 33, 34, 37 and 41 now depend from claims 45 or 46, which are limited to intravenous administration of an anti-CD20 antibody. Such administration has been noted by the Examiner as not disclosed in Davis et al. Accordingly, the Applicants respectfully request withdrawal of this rejection.

3. EP0332865 in view of U.S. Patent No. 5,736,137

Claims 1, 6-10, 12-16, 22, 28, 32, 34-41 and 43-60 stand rejected under 35 U.S.C. § 103(a) as obvious over EP0332865 ("Meyer et al."), viewed in light of U.S. Patent No. 5,736,137 ("Anderson et al."). In particular, the Examiner asserts that Meyer et al. teaches the use of an anti-B cell antibody to treat transplant rejection (citing columns 2 and 3, last two paragraphs – the Applicants assume the Examiner refers to the last paragraphs of *pages* 2 and 3, since Meyer et al. does not appear to provide column numbering). *See* Office Action, page 9. The Examiner notes that Meyer et al. does not teach anti-CD20 antibodies or uses thereof. *See id.* Anderson et al. is cited for teaching chimeric anti-CD20 antibodies and their use in "treatment" to deplete B cells *in vivo*. *See id.* Anderson et al. is also cited for teaching dosages of an anti-CD20 antibody that "are less than 375 mg/ patient." *See id.* Based on these asserted teachings, the Examiner indicates that it would have been obvious "to have created the claimed invention." *See id.* According to the Examiner, one of skill in the art would have been motivated to create the claimed invention "because Meyer et al. teach that the anti B cell antibody used can be chimeric

and is cytotoxic to B cells, while Anderson et al. teach that C2B8 chimeric antiCD20 antibody effectively depletes B cells when administered in vivo." Office Action, page 9.

Meyer et al. describes a method for preventing an adverse immune reaction in a patient to a concurrently or subsequently administered therapeutic agent. The therapeutic agent is not an anti-B cell antibody, and is specifically not an anti-CD20 antibody. As Meyer et al. explains, the "B-cell" antibody is administered to suppress the response of the immune system to the subsequently or concurrently administered agent that might otherwise trigger such an immune response. *See, e.g.,* Meyer et al. at page 2, lines 35-43 ("The antibody is administered in an amount sufficient to suppress the response of the B-lymphocytes to concurrent, subsequent, or prior administration to the mammal of diagnostic or therapeutic doses of, unmodified antibodies or antibody fragments, or conjugates thereof with therapeutic or diagnostic agents such as radioisotopes, toxins, cytotoxic agents, or the like; or to other therapeutic or diagnostic non-antibody foreign proteins."). The Examiner's characterization of Meyer et al., therefore, overlooks critical distinctions between the presently claimed process and the Meyer et al. disclosure.

For example, Meyer et al. teaches that the other agent (not the "anti-B cell" antibody) will treat the disorder. Nowhere in Meyer et al. is it suggested that administration of "anti-B cell" antibodies of any type would in any way be used, useful or effective in blocking an immune response to an allogeneic graft, or treating graft-versus-host or host-versus-graft disease in a human. In the case of "organ transplant rejection," Meyer et al. notes that "murine derived anti-T lymphocyte OKT-3 antibody" is used as the transplant rejection treatment and the need for the anti-B cell antibody is due to the "strong B-lymphocyte response to the mouse antibody [(OKT-

3)], which, at least in part compromises" the efficiency of the OKT-3 treatment. *See* Meyer et al. at page 3, lines 49-54. Thus, OKT-3 is used to treat transplant rejection and the anti-B cell antibody is used to minimized the impact of the adverse B cell response to the use of the mouse OKT-3 antibody, not the transplant. Meyer et al's teachings that a distinct therapeutic agent other than the "anti-B cell" antibodies must be used as the therapeutic agent suggests that Meyer et al., like others in the field, would not have expected an anti-B cell antibody, and particularly a specific anti-B cell antibody (i.e., an anti-CD20 antibody), would provide therapeutic benefits in blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease.

Meyer et al. indicates that the goal of suppressing the response by B-lymphocytes to the foreign antigenic agent is to be made possible using antibodies to mature B-cell antigens. However, Meyer et al. does not suggest that any particular sub-population of mature B-lymphocytes is the target of the process. Instead, it appears that the Meyer et al. process is designed to suppress any response by any type of B-lymphocyte in the patient. For example, Meyer et al. provides that:

> Since it is possible that in some, if not in many or all cases, the B-lymphocyte population may not all share the same surface marker, it may be necessary to utilize more than one antibody to effectively achieve the desired suppression of the B-lymphocyte response. This invention envisions the utilization of as many antibodies as necessary to accomplish this goal.

In contrast, the presently claimed invention requires the use of an antibody that will specifically target only that sub-population of B-lymphocytes that express the CD20 antigen. And, in contrast to the Meyer et al. teaching of the need for a complete B-cell depletion strategy (e.g., to be achieved by using multiple anti-B cell antibodies, each binding to distinct antigens and

affecting different B-cell populations), the selective depletion of only B-lymphocytes expressing CD20 is, as the claims require, the means by which the desired therapeutic effects of blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease are realized.

Meyer et al. also provides a description of only two antibodies (the Lym-1 and Lym-2 antibodies). These are the only examples of antibodies in the described processes. These two antibodies do not bind the CD20 antigen found on B-lymphocytes, and thus bind to a different B-cell population relative to B-cells that express CD20. Because there is no suggestion, statement or other direction in the Meyer et al. publication to use antibodies that selectively bind the CD20 antigen, as required by the present claims, Meyer et al. cannot be viewed as specifically suggesting the use of anti-CD20 antibodies, much less processes for blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease through depletion of the CD20+ circulating B-lymphocyte population. Instead, because Meyer et al. suggests that its method will require suppression of any B-lymphocyte response to the concurrently or subsequently administered therapeutic agent, it affirmatively teaches away from the use of any particular type of antibody that binds to a specific antigen found on B-lymphocytes. Thus, rather than providing a suggestion to focus on a particular sub-population of B-lymphocytes, Meyer et al. suggests precisely the opposite – targeting the entire mature B-cell population.

Thus, because the purpose and effects from administration of the Meyer et al. process are different than those of the presently claimed methods, one cannot reasonably equate the process or physiological effects that might be associated with administration of the Lym-1 and Lym-2

antibodies with the selective depletion observed with the administration of antibodies that bind to the CD20 antigen. Given that the physiological effects of administering any particular type of B-cell specific antibody will be unique to the particular antigenic determinant recognized by the antibody being administered, different therapeutic effects will be observed when Lym-1 and Lym-2 antibodies are administered to a human relative to when anti-CD20 antibodies are administered to a patient at least because different populations of cells will be targeted and affected by the different antibodies. This, in turn, will have a significant impact on the potential therapeutic effects of administering the antibody to the patient. In view of these considerations, it is scientifically implausible to suggest or assume that the same physiological effects will be observed regardless of the antigenic specificity of the "anti-B cell" antibody being used.

The numerous distinctions between the Meyer et al. publication and the presently claimed invention render Meyer et al. inapplicable to the presently claimed methods. Specifically, a person of skill in the art would not find Meyer et al. to provide any disclosure or suggestion to use antibodies that bind to the CD20 antigen, would not find any motivation to use these antibodies in the presently claimed methods, and would not have found Meyer et al. to be relevant to the presently claimed methods which target a particular B-lymphocyte population to block an immune response to an allogeneic graft or treat graft-versus-host or host-versus-graft disease.

The Examiner also suggests that a person of skill in the art would be motivated to modify the Lym-1/Lym-2 antibody based methods disclosed in Meyer et al. to obtain the presently claimed methods. The Examiner's motivation theory is premised on an incorrect set of assumptions. For example, the Examiner suggests that "Meyer et al. teach that antibody against

B cell surface marker can be administered to treat transplant rejection." Office Action, page 9. The cited passages do not teach treatment of transplant rejection with anti-B-cell antibodies, much less treatment with the specific anti-CD20 antibodies of the present claims. In contrast, as discussed above, the purpose, objective, and parameters of Meyer et al. for administering an agent to block a B-cell response are fundamentally different from the approach required by the present claims, where a particular anti-B-cell antibody is being administered to directly treat the disorder in question (e.g., a native immune response to the graft). And, critically, the "same results" will not inherently ensue from administration of Lym-1 or Lym-2 antibodies, or generically any anti-B cell antibody, relative to the results observed when anti-CD20 antibodies are administered. As such, even if the cited reference taught each limitation of the present claims and the motivation theory advanced by the Examiner to modify Meyer et al. were sufficient, one of skill in the art would not have had a reasonable expectation of success in achieving the presently claimed methods if the antibodies of Meyer et al. were replaced with specific anti-CD20 antibodies.

In conclusion, Applicants observe that the presently elected claims are limited to methods of blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease using a specific antibody (anti-CD20) which is administered in a particular manner (i.e., more than one intravenous administration). Meyer et al. does not teach use of anti-CD20 antibodies for any purpose, does not teach use of anti-CD20 to block an immune response to an allogeneic graft or treat graft-versus-host or host-versus-graft disease, and does not teach administration of "B-cell" antibodies through multiple intravenous injections. Applicant's also submit that Meyer et al. does not establish or suggest that the presently claimed methods would

have been viewed as having been "obvious" to a person of skill in the art, and as such, cannot be used, alone or in conjunction with Anderson et al., to reject the claims under §103.

For these reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a) over the combination of Meyer et al. and Anderson et al.

4. Meyer et al. in view of Anderson et al., and further in view of Gehlsen and Davis et al.

Claims 10, 33 and 42 stand rejected under 35 U.S.C. § 103(a) as obvious over Meyer et al., viewed in light of Anderson et al., and further in view of Gehlsen, and viewed further in light of Davis et al. Though the Examiner does not specifically list Davis et al. in the introduction of this rejection, this reference is cited in the reasoning behind the rejection (i.e., "the '281 publication").

With regard to Gehlsen, the Examiner asserts that this reference teaches "^{131}I labeled anti-B1 (Bexxar) mAb, raised to the CD-20 antigens that are expressed on the surface of mature B-cells," and that this "is one example of a radiolabeled mAb that has seen successful in treating follicular non-Hodgkin's lymphoma in recent clinical trials." Office action, page 10 (referring to Gehlsen at col. 9, lines 19-30). The Examiner indicates that it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the monoclonal antibody to human CD20 taught by Davis et al. with the ^{131}I-B1 antibody as taught by Gehlsen. The Examiner explains that the motivation to make such a substitution is "because ^{131}I-B1 has been successful in vivo in humans." Office Action, page 10. This "success," however, was noted in clinical trials treating follicular non-Hodgkin's lymphoma. *See* Gehlsen at col. 9, lines 24-9.

The Examiner's rationale in citing the Meyer et al. and Anderson et al. references in this rejection is presumably the same as that employed in the rejection of claims 1, 6-10, 12-16, 22, 28, 32, 34-41 and 43-60, since the Examiner has not provided independent reasons for why these references render obvious claims 10, 33, and 42. Moreover, although the Examiner has provided a reason for the Gehlsen/Davis et al. combination, no reasoning has been provided for the combination of Gehlsen and Davis et al. with Meyer et al. and Anderson et al. Thus, the Examiner has not explained the basis for the combination of each of the four cited reference. *See, e.g.*, MPEP § 706.02(j). For example, while the Examiner has explained that it would have been purportedly obvious to substitute the monoclonal antibody to human CD20 taught by Davis et al. with the ^{131}I-B1 antibody as taught by Gehlsen, no explanation of how these aspects of Davis et al. and Gehlsen fit together with the assorted teachings of Meyer et al. and Anderson et al. in a manner that renders obvious the present claims. Accordingly, the Applicants respectfully submit that the Examiner has not set forth a *prima facie* case of obviousness of the present claims. *See, e.g.*, MPEP §§ 706.02(j); 2142, 2143. Withdrawal of this rejection is respectfully requested on this basis as well as the remarks below.

Initially, the Applicants respectfully submit that, as discussed above, Meyer et al. and Anderson et al. do not render the methods recited in claims 1, 6-10, 12-16, 22, 28, 32, 34-41 and 43-60 obvious, and as such does not address each limitation of the present claims. For example, the primary reference, Meyer et al., does not teach (1) the use of anti-CD20 antibodies for any purpose, (2) the use of anti-CD20 to block an immune response to an allogeneic graft or treat graft-versus-host or host-versus-graft disease, and (3) administration of anti-CD20 antibodies through multiple intravenous injections. Anderson et al. does not cure these deficiencies.

Gehlsen is directed to methods of treating cancer by administering histamine together with a conventional cancer therapy such as surgery, radiation, immunotherapy, or an agent that enhances the humoral response of the patient. Thus, Gehlsen is also directed to the treatment of cancerous conditions, specifically non-Hodgkin's lymphoma, but fails to provide any teaching regarding methods for blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease. Gehlsen therefore does not suggest or provide a reasonable expectation of success in extrapolating the use of an anti-CD20 antibody in the currently claimed methods. As such, Gehlsen does not cure the deficiencies of the rejections premised on Meyer et al., and Andersen.

Davis et al. is directed to treating immune cell mediated systemic diseases by administering a first non-therapeutic dose of an antibody followed by subsequent subcutaneous administration of the antibody. This reference does not teach a method in which an anti-CD20 antibody is administered exclusively via an intravenous means to block an immune response to an allogeneic graft or treat graft-versus-host or host-versus-graft disease. Moreover, this reference provides no objective information that would have provided a reasonable expectation of success in extrapolating the anti-CD4 T-cell specific examples provided therein to the use of a B-cell specific anti-CD20 antibody in its methods, let alone in the methods of the present claims.

For these reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a) over the combination of Meyer et al. and Anderson et al. in view of Davis et al. and Gehlsen.

Rejection Under 35 U.S.C. § 102(a)

Claims 1, 6-7, 13, 22, 45, 47 and 49-50 stand rejected under 35 U.S.C. § 102(a) as anticipated by Perrotta et al. The Examiner did not specifically identify this reference by anything other than a name. The Applicants assume, therefore, that the Examiner refers to Perrotta & Abuel, Blood 92(10 Suppl. 1, Part 1-2):88b (abstract # 3360) (Nov. 1998) ("Perrotta") in the present rejection.

The Examiner begins the basis of this rejection by stating that "the claims under consideration encompass a method of blocking an immune response in a human that has not received a graft." Office Action, page 10. This position is untenable since it conflicts with explicit claim language. Rather, the claims specify that the immune response to be blocked is in response to an allogeneic graft in a human. Claim 22 specifies administering the antibody before the human is exposed to the allogeneic graft, but exposure to the allogeneic graft is a prerequisite to the immune response being treated in the human. Perrotta reports administration of rituximab to a single patient afflicted with a bleeding disorder – idiopathic thrombocytopenic purpura (ITP). Perrotta does not indicate that the ITP patient had received an allogeneic graft or was experiencing an immune response to an allogeneic graft. Perrotta therefore certainly does not teach or suggest administration of an anti-CD20 antibody to block an immune response to an allogeneic graft.

Since Perrotta fails to each element of the rejected claims, this reference cannot anticipate these claims. Accordingly, the Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102(e)

Claims 1, 6-10, 13-15, 22, 32-36, 43, 45 and 47-53 stand rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent Application Publication No. 2003-0133930 ("Goldenberg et al.").

The Examiner suggests, in setting forth this rejection, that "the claims under consideration encompass a method of blocking an immune response in a human that has not received a graft." Office Action, page 11. Again, this position is untenable since it conflicts with explicit claim language.

The Examiner further explains that "Goldenberg et al. disclose intravenous treatment of patients with anti-CD20 antibody including C2B8 or I131 labeled B1 at dosages encompassed by those recited in the claims because it is the same antibody as recited in the claims (see [0089, claims 1,2,12, [0004]), administered at the same concentration." Office Action, page 11. The Examiner's position, therefore, hinges on the purported disclosure of the use of anti-CD20 antibody in the methods of Goldenberg et al.

Goldenberg et al. was filed January 24, 2003 and claims priority to continuation application No. 09/590,284, filed June 9, 2000, which claims priority to U.S. provisional application No. 60/138,284 ("the '284 application"), filed June 9, 1999. The present application was filed July 10, 2000 and claims priority to a provisional application filed July 16, 1999. Accordingly, in order to anticipate the present claims, the '284 application must disclose the anticipating subject matter in a manner that would be sufficient for a priority claim. The Applicants include herewith a copy of the '284 application, as filed, for reference purposes.

Review of the '284 application reveals no disclosure whatsoever of the use of an anti-CD20 antibody in the methods described therein. The disclosure is limited to anti-CD22 antibodies. The background section (page 1) notes the existence of anti-CD20 antibodies used for treating B cell lymphomas such as non-Hodgkin's lymphoma, and explains that these antibodies have not shown objective responses in intermediate and aggressive lymphomas. This is the only mention of anti-CD20 antibodies in the '284 application. This section provides no mention or suggestion of the use of an anti-CD20 antibody in blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease. Therefore, the use of anti-CD20 antibody in the methods of Goldenberg et al. does not find support in the '284 application and therefore Goldenberg et al. is not prior art in this regard. On this basis alone the Examiner may withdraw this rejection.

In addition, similar to the '284 application, Goldenberg et al. is directed to treating autoimmune disorders. Though numerous autoimmune disorders are listed, blocking an immune response to an allogeneic graft or treating graft-versus-host or host-versus-graft disease are not. Accordingly, this reference fails to teach each element of the rejected claims. Accordingly, the Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicants respectfully submit that all pending and elected claims as currently presented are in condition for allowance. If, for any reason, the Examiner disagrees, he is requested to contact the undersigned attorney at 202-736-8914 in an effort to resolve any matter still outstanding *before* issuing another action. Favorable reconsideration is respectfully requested.

In the unlikely event that the Patent Office determines that extensions and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or fees due to our Deposit Account No. 18-1260, referencing Docket No. 22338-00602. Any refund should be credited to the same account. The Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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Rituxan®

Rituximab

WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of Rituxan infusion have been reported. These fatal reactions followed an infusion reaction complex, which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See **WARNINGS** and **ADVERSE REACTIONS.**)

Patients who develop severe infusion reactions should have Rituxan infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) patients with Rituxan. (See **WARNINGS.**)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with Rituxan treatment. (See **WARNINGS** and **ADVERSE REACTIONS.**)

DESCRIPTION

The Rituxan® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab Drug Product is manufactured from bulk Drug Substance manufactured by Genentech, Inc. (US License No. 1048).

Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1,2] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)[3] but is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[2]

B-cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B-cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T cell activation, and/or pro-inflammatory cytokine production.[7]

Preclinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[8] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[9]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

Pharmacokinetics

In patients with NHL given single doses at 10, 50, 100, 250 or 500 mg/m² as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose.[10] In 14 patients given 375 mg/m² as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion.[11,12,13] The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

Rituxan at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 4 doses to 203 patients with NHL naive to Rituxan.[13,14] The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5–996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.[11,14] Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

Rituxan at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for 8 doses to 37 patients with NHL.[15] The mean C_{max} after 8 infusions was 550 µg/mL (range, 171–1177 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion (Table 1).

Table 1
Rituximab C_{max} Values

Infusion Number	Mean C_{max} µg/mL	Range µg/mL
1	242.6	16.1–581.9
2	357.5	106.8–947.6
3	381.3	110.5–731.2
4	460.0	138.0–835.4
5	475.3	156.0–929.1
6	515.4	152.7–865.2
7	544.6	187.0–936.8
8	550.0	170.0–1177.0

The pharmacokinetic profile of Rituxan when administered as 6 infusions of 375 mg/m² in combination with 6 cycles of CHOP chemotherapy was similar to that seen with Rituxan alone.[16]

Following the administration of 2 doses of Rituximab in patients with rheumatoid arthritis, the mean C_{max} values were 183 mcg/mL (CV=24%) for the 2 x 500 mg dose and 370 mcg/mL (CV=25%) for the 2 x 1000 mg dose, respectively. Following 2 x 1000 mg Rituximab dose, mean volume of distribution at steady state was 4.3 L (CV=28%). Mean systemic serum clearance of Rituximab was 0.01 L/h (CV=38%), and mean terminal elimination half-life after the second dose was 19 days (CV=32%).

Special Populations

Gender: The female patients with RA (n=86) had a 37% lower clearance of Rituximab than male patients with RA (n=25). The gender difference in Rituximab clearance does not necessitate any dose adjustment because safety and efficacy of Rituximab do not appear to be influenced by gender.

The pharmacokinetics of Rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of Rituximab.

Pharmacodynamics

Administration of Rituxan resulted in a rapid and sustained depletion of circulating and tissue-based B-cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in seven of eight patients with NHL who had received single doses of Rituximab ≥100 mg/m².[10] Among the 166 patients in the pivotal NHL study, circulating B-cells (measured as CD19-positive cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients.[13] Of the responding patients assessed (n=80), 1% failed to show significant depletion of CD19-positive cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately 6 months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.[13]

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.[13]

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with all patients demonstrating near complete depletion within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months, followed by subsequent gradual recovery after that timepoint. A small proportion of patients (4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

In RA studies, total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. However, mean immunoglobulin levels remained within normal levels over the 24-week period. Small proportions of patients experienced decreases in IgM (7%), IgG (2%), and IgA (1%) levels below the lower limit of normal. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

Treatment with Rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP) and RF.

CLINICAL STUDIES

Relapsed or Refractory, Low Grade or Follicular, CD20-Positive, B-Cell NHL

Rituxan regimens tested include treatment weekly for 4 doses and treatment weekly for 8 doses. Results for studies with a collective enrollment of 296 patients are summarized below (Table 2):

Table 2
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting
(See ADVERSE REACTIONS for Risk Factors Associated with Increased Rates of Adverse Events)

	Study 1 Weekly x 4 N=166	Study 2 Weekly x 8 N=37	Study 1 and Study 3 Bulky Disease, Weekly x 4 N=39[a]	Study 3 Retreatment, Weekly x 4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b,c,d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[a] Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.
[b] Kaplan-Meier projected with observed range.
[c] "+" indicates an ongoing response.
[d] Duration of response: interval from the onset of response to disease progression.

Weekly for 4 Doses

Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular B-cell NHL who received 375 mg/m² of Rituxan given as an IV infusion weekly for 4 doses.[14] Patients with tumor masses >10 cm or with >5000 lymphocytes/µL in the peripheral blood were excluded from the study. Results are summarized in Table 2. The median time to onset of response was 50 days and the median duration of response was 11.2 months (range, 1.9–42.1+). Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF subtype A (58% vs. 12%), higher in patients whose largest lesion was < 5 cm vs. > 7 cm (maximum, 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared with chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following adverse prognostic factors were *not* associated with a lower response rate: age ≥60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

Weekly for 8 Doses

Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low grade NHL received 375 mg/m² of Rituxan weekly for 8 doses. Results are summarized in Table 2. (See **ADVERSE REACTIONS: Risk Factors Associated with Increased Rates of Adverse Events.**)

Bulky Disease, Weekly for 4 Doses

In pooled data (Study 1 and 3) from multiple studies of Rituxan, 39 patients with relapsed or refractory, bulky disease (single lesion >10 cm in diameter), low grade NHL received 375 mg/m² of Rituxan weekly for 4 doses. Results are summarized in Table 2.[14,17] (For information on the higher incidence of Grade 3 and 4 adverse events, see **ADVERSE REACTIONS: Risk Factors Associated with Increased Rates of Adverse Events.**)

Retreatment Weekly for 4 Doses

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m² of Rituxan weekly for 4 doses.[18] All patients had relapsed or refractory, low grade or follicular B-cell NHL and had achieved an objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these 60 patients, 55 received their second course of Rituxan, 3 patients received their third course and 2 patients received their second and third courses of Rituxan in this study. Results are summarized in Table 2.

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m² on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. Of the 289 patients with available histologic material for review, 95% had a centrally-confirmed diagnosis of follicular (REAL follicular grade 1, 2 and 3) NHL. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 3. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 3
Efficacy Results in Study 4

	Study Arm	
	CVP	R-CVP
Median PFS (years)[a]	1.4	2.4
Hazard ratio (95% CI)[b]	0.44 (0.29, 0.65)	

[a] $p < 0.0001$, two-sided stratified log-rank test.
[b] Estimates of Cox regression stratified by center.

Previously Treated, Low-Grade, CD20-Positive, B-Cell NHL

Study 5

A total of 322 patients with previously untreated low-grade, B-cell NHL (IWF Grades A, B or C) who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan 375 mg/m² IV infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2. Among the 237 patients for whom histologic material was available for review, 201 patients (85%) had centrally confirmed IWF Grade A, B or C NHL.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of Rituxan were evaluated in three, randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 6

A total of 632 patients aged ≥60 years with B-cell NHL Grade F, G, or H by the International Working Formulation classification or DLBCL (including primary mediastinal B-cell lymphoma) in the REAL classification were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients were given 6 or 8, 21 day cycles of CHOP. Patients in the R-CHOP arm also received 4 or 5 doses of Rituxan 375 mg/m² on Days -7 and -3 (prior to Cycle 1), and 48–72 hours pre-Cycle 3, pre-Cycle 5, and pre-Cycle 7 for patients receiving 8 cycles of CHOP induction. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥2, 86% had ECOG performance status of <2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 4. These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given after the second randomization.

Analysis of results after the second randomization in Study 6 demonstrates that for patients randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

Study 7

A total of 399 patients with DLBCL, aged ≥60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m² on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥2, 80% had ECOG performance status scores <2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 4.

Study 8

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤1, 99% had ECOG performance status of <2, 29% had elevated LDH levels, 49% had bulky disease and 34% had extranodal involvement. Efficacy results are presented in Table 4.

Table 4
Efficacy Results in Studies 6, 7, and 8

	Study 6 (n=632)		Study 7 (n=399)		Study 8 (n=823)	
	CHOP	R-CHOP	CHOP	R-CHOP	Chemo	R-Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	1.6	3.1	1.1	2.9	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	63%	74%	58%	69%	86%	95%
Hazard ratio[d]	0.72[a]		0.68[a]		0.40[a]	

[a] Significant at $p<0.05$, 2-sided.
[b] NE=Not reliably estimable.
[c] Kaplan-Meier estimates.
[d] R-CHOP vs. CHOP.

In Study 7, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

Rheumatoid Arthritis (RA)

The efficacy and safety of Rituxan were evaluated in 517 patients with active disease who were receiving methotrexate and had a prior inadequate response to at least one TNF inhibitor. Patients were ≥18 years, diagnosed with RA according to American College of Rheumatology (ACR) criteria and had at least 8 swollen and 8 tender joints. Patients received 2 doses of either Rituxan 1000 mg or placebo as an IV infusion on days 1 and 15, in combination with continued methotrexate 10–25 mg weekly.

Efficacy was assessed at 24 weeks. Glucocorticoids were given IV as premedication prior to each Rituxan infusion and orally on a tapering schedule from baseline through Day 16.

The proportions of Rituxan (1000 mg) treated patients achieving ACR 20, 50, and 70 responses in this study is shown in Table 5.

Table 5
ACR Responses at Week 24 in Placebo-Controlled Study
(Percent of Patients) (Modified Intent-to-Treat Population)

Response	Placebo + MTX n=201	Rituxan + MTX n=159
ACR 20	18%	51% p<0.0001
ACR 50	5%	27% p<0.0001
ACR 70	1%	12% p<0.0001

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 6.

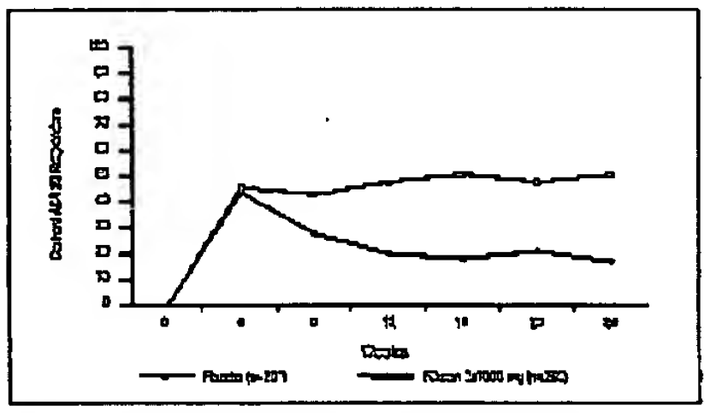
Table 6
Components of ACR Response
(Modified Intent-to-Treat Population)

	Placebo + MTX n=201		Rituxan + MTX n=206	
Parameter (median)	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	33.0	27.0	33.0	13.0*
Swollen Joint Count	20.0	19.0	21.0	9.5*
Physician Global Assessment*	71.0	60.0	71.0	38.0*
Patient Global Assessment*	73.0	58.0	71.0	41.0*
Pain*	69.0	58.0	67.0	38.0*
Disability Index (HAQ)*	2.0	1.9	1.9	1.5*
CRP (mg/dL)	2.4	2.5	2.8	0.9*

*Visual Analogue Scale: 0=best, 100=worst.
†Disability Index of the Health Assessment Questionnaire: 0=best, 3=worst.
*p≤0.01, Rituxan + MTX vs. Placebo + MTX.

The time course of ACR 20 response for this study is shown in Figure 1. Although both treatment groups received a brief course of IV and oral glucocorticoids, resulting in similar benefits at week 4, higher ACR 20 responses were observed for the Rituxan group by week 8 and were maintained through week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 1
ACR 20 Responses Over 24 Weeks



While the efficacy of Rituxan was supported by two well-controlled trials in RA patients who had inadequate responses to non-biologic DMARDs, but who had not failed TNF antagonist therapy, a favorable risk benefit relationship has not been established in this population (See PRECAUTIONS.)

INDICATIONS AND USAGE
Non-Hodgkin's Lymphoma
Rituxan® (Rituximab) is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma.

Rituxan® (Rituximab) is indicated for the first-line treatment of follicular, CD20-positive, B-cell non-Hodgkin's lymphoma in combination with CVP chemotherapy.

Rituxan® (Rituximab) is indicated for the treatment of low-grade, CD20-positive, B-cell non-Hodgkin's lymphoma in patients with stable disease or who achieve a partial or complete response following first-line treatment with CVP chemotherapy.

Rituxan® (Rituximab) is indicated for the first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens.

Rheumatoid Arthritis
Rituxan® (Rituximab) in combination with methotrexate is indicated to reduce signs and symptoms in adult patients with moderately- to severely-active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

CONTRAINDICATIONS
None.

WARNINGS (See BOXED WARNINGS)
Severe Infusion Reactions (see BOXED WARNINGS and ADVERSE REACTIONS)

Rituxan has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituxan administration. The most severe manifestations also reported include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and anaphylactic and anaphylactoid events. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The Rituxan infusion should be interrupted for severe reactions. Medications and supportive care measures including, but not limited to, epinephrine, antihistamines, glucocorticoids, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen, should be available for immediate use and instituted as medically indicated for use in the event of a reaction during administration. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (≥25,000/mm³) with or without evidence of high tumor burden. (See WARNINGS: Cardiovascular and ADVERSE REACTIONS.)

Tumor Lysis Syndrome (TLS) (See BOXED WARNINGS and ADVERSE REACTIONS)
Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hyperuricemia, or hyperphosphatemia, have been reported within 12–24 hours after the first Rituxan infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with Rituxan in patients with NHL. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells (≥25,000/mm³) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, Rituxan has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections
Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with Rituxan. The majority of patients received Rituxan in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of Rituxan and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of Rituxan. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following Rituxan therapy. In patients who develop viral hepatitis, Rituxan and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming Rituxan therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus (progressive multifocal leukoencephalopathy (PML)), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of Rituxan and have resulted in death.

Cardiovascular
Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of Rituxan. Patients with pre-existing cardiac conditions including arrhythmias and angina have had recurrences of these events during Rituxan therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal (See BOXED WARNINGS: Tumor Lysis Syndrome (TLS) and ADVERSE REACTIONS)
Rituxan administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome in hematologic malignancy patients. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm³) or high tumor burden who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of Rituxan should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions (See BOXED WARNINGS)
Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with Rituxan. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),* Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1–13 weeks following Rituxan exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of Rituxan to patients with any of these mucocutaneous reactions has not been determined.

Concomitant use with biologic agents and DMARDs other than methotrexate
In RA: Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in patients exhibiting peripheral B cell depletion following treatment with Rituximab. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used concomitantly.

Bowel Obstruction and Perforation
Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving Rituxan in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range: 1–77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

PRECAUTIONS
Information for Patients
Patients should be provided the Rituxan Patient Information leaflet and provided an opportunity to read it prior to each treatment session. Because caution should be exercised in administering Rituxan to patients with active infections, it is important that the patient's overall health be assessed at each visit and any questions resulting from the patient's reading of the Patient Information be discussed.

Laboratory Monitoring
Because Rituxan targets all CD20-positive B lymphocytes (malignant and nonmalignant), complete blood counts (CBC) and platelet counts should be obtained at regular intervals during Rituxan therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by Rituxan can extend well beyond the treatment period.

Drug/Laboratory Interactions
There have been no formal drug interaction studies performed with Rituxan. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS: Renal.) In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of Rituximab.

Immunization
The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

Physicians should review the vaccination status of patients with RA being considered for Rituxan treatment and follow the Centers for Disease Control and Prevention (CDC) guidelines for adult vaccination with non-live vaccines intended to prevent infectious disease, prior to therapy. For patients with NHL, the benefits of primary and/or booster vaccinations should be weighed against the risks of delay in initiation of Rituxan therapy.

Use in patients with RA who have had an prior inadequate response to TNF antagonists:
While efficacy of Rituxan was supported in two well-controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, a favorable risk benefit relationship has not been established in this population. The use of Rituxan in patients with RA who have no prior inadequate response to one or more TNF antagonists is not recommended (see CLINICAL STUDIES: Rheumatoid Arthritis).

Retreatment in patients with RA: Safety and efficacy of retreatment have not been established in controlled trials. A limited number of patients have received two to five courses (two infusions per course) of treatment in an uncontrolled setting. In clinical trials in patients with RA, most of the patients who received additional courses did so 24 weeks after the previous course and none were retreated sooner than 16 weeks.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
No long-term animal studies have been performed to establish the carcinogenic potential of Rituxan. Studies also have not been completed to assess mutagenic potential of Rituxan, or to determine potential effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following Rituxan therapy.

Pregnancy Category C
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Animals were administered Rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on post-coitum days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in exposures of 0.8-fold a human 2 g dose based on AUC. Although Rituximab has been shown to cross the monkey placenta, there was no evidence of teratogenicity under the conditions of the experiment.

Noninteratogenic effects: Results from the embryo-fetal developmental toxicology study described above showed that Rituximab treatment produced a decrease in lymphoid tissue B-cells in the offspring of treated dams.

A subsequent pre- and postnatal developmental toxicity study in cynomolgus monkeys was completed to assess developmental toxicity and the recovery of B-cells and immune function in infants exposed to Rituximab *in utero*. Rituximab was administered from early gestation (post-coitum day 20) through lactation (post-partum day 28). Due to the possibility of anti-drug antibody development with such a long dosing period, the animals were divided into 3 sets of dosing periods: one set received Rituximab (20 or 100 mg/kg weekly) from post-coitum day 20 through delivery and post-partum day 28 (~25 weeks); a second set received Rituximab (20 or 100 mg/kg weekly) from post-coitum day 50 through post-coitum day 76 (8 weeks); a third set received Rituximab (20 or 100 mg/kg weekly) from post-coitum day 76 through delivery and post-partum day 28 (~8 weeks). For each of these dosing periods, a loading dose was administered for the first 5 days of the period at doses of 15 or 75 mg/kg/day. The decreased B-cells and immunosuppression noted in the offspring of pregnant animals treated with other 20 or 100 mg/kg/week Rituximab showed a return to normal levels and function within 6 months post-birth. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human responses, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Rituximab was excreted in the milk of lactating cynomolgus monkeys. It is not known whether Rituxan is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use
The safety and effectiveness of Rituxan in pediatric patients have not been established.

Geriatric Use
Among patients with DLBCL in three randomized, active-controlled trials, 927 patients received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these subjects and younger subjects. However, elderly patients were more likely to experience cardiac adverse events, mostly supraventricular arrhythmias. Serious pulmonary adverse events were also more common among the elderly, including pneumonia and pneumonitis.

Clinical studies of Rituxan in previously untreated, low-grade or follicular, CD20-positive, B-cell NHL and in relapsed or refractory, low-grade or follicular lymphoma did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Among the 517 patients in the phase 3 RA study, 16% were 65–75 years old and 2% were 75 years old and older. The Rituxan ACR 20 response rates in the older (age ≥65 years) vs. younger (age <65 years) patients were similar (53% vs. 51%, respectively). Adverse reactions, including incidence, severity, and type of adverse reaction were similar between older and younger patients.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The following serious adverse reactions, some with fatal outcomes, have been reported in patients treated with Rituxan (see BOXED WARNINGS and WARNINGS): severe or fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

Adverse Reactions in Patients with Non-Hodgkin's Lymphoma
The overall safety database for Rituxan is based on clinical trial data from 1600 patients with NHL, who received Rituxan either as a single agent or in combination with chemotherapy. Additional safety information was obtained from post-marketing safety surveillance. The most common adverse reactions were infusion reactions (see INFUSION REACTIONS below).

Except as noted, adverse events described below occurred in the setting of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, NHL and are based on 356 patients treated in single-arm studies of Rituxan administered as a single agent. Most patients received Rituxan 375 mg/m² weekly for 4 doses.

Infusion Reactions (See BOXED WARNINGS and WARNINGS)
Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first Rituxan infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion). Infusion site pain was reported in less than 5% of patients.

Infectious Events (See WARNINGS: Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections)
Rituxan induced B-cell depletion in 70% to 80% of patients with NHL and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1–488 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 0% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Hematologic Events
Grade 3 and 4 cytopenias were reported in 48% of patients treated with Rituxan; these include: lymphopenia (40%), neutropenia (5%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1–589 days) and of neutropenia was 13 days (range, 2–116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy were reported.

Pulmonary Events

135 patients (38%) experienced pulmonary events in clinical trials. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical studies and post-marketing surveillance, there have been a limited number of reports of bronchiolitis obliterans presenting up to 6 months post-Rituxan infusion and a limited number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3 months post-Rituxan infusion, some of which resulted in fatal outcomes. The safety of resumption or continued administration of Rituxan in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immunogenicity

The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

In clinical studies of patients with low-grade or follicular NHL receiving single-agent Rituxan, human antichimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients and 3 had an objective clinical response. These data reflect the percentage of patients whose test results were considered positive for antibodies to Rituxan using an enzyme-linked immunosorbent assay (limit of detection=7 ng/mL).

Single Agent Rituxan for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The data below were obtained in 356 patients receiving single agent Rituxan for treatment of relapsed, refractory, low-grade or follicular NHL (see **CLINICAL STUDIES**). The majority of patients received 375 mg/m² IV weekly x 4 doses. The median age was 57 (range 22–81 years). Sixty percent were male; 93% were Caucasian, 1% were Black, 2% were Hispanic, 2% were Asian, and 2% were from other racial groups.

Table 7 lists the most common, as well as Grade 3 and 4, adverse events observed.

Table 7
Incidence of Adverse Events in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

[a] Adverse Events observed up to 12 months following Rituxan.
[b] Adverse Events graded for severity by NCI-CTC criteria[a].

Risk Factors Associated With Increased Rates of Adverse Events

Administration of Rituxan weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[a] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with Rituxan compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥ 10 cm) (N = 39) versus patients with lesions <10 cm (N=195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

The safety data were obtained in a single, multi-center, randomized study of 321 patients of whom 162 received Rituxan in combination with CVP chemotherapy (R-CVP) and 159 received CVP chemotherapy alone (CVP). Eighty-five percent of R-CVP patients received the maximum number of doses (8) of Rituxan. The median age was 52 years, 54% were male, and 98% were Caucasian.

Patients in the R-CVP arm had higher incidences of infusional toxicity and of neutropenia as compared to those in the CVP arm. The following adverse events occurred more frequently (≥5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%).

Previously Untreated, Low-Grade, CD20-Positive, B-Cell NHL

Safety data were obtained in a single, multi-center, randomized study of 322 patients of whom 161 received Rituxan and 161 received no treatment following 6–8 cycles of CVP chemotherapy. Ninety-five patients (59%) received the maximum number of doses (16) of Rituxan.

The median age for the Rituxan treated patients was 58 years. Fifty-five percent were male, 93% were Caucasian, and 5% Black.

The following adverse events were reported more frequently (≥5%) in patients receiving Rituxan following CVP compared with those who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse event that occurred more frequently (≥2%) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%).

Rituxan in Combination with Chemotherapy for DLBCL

Adverse events described in the setting of DLBCL are based on three randomized, active-controlled clinical trials in which 927 patients received Rituxan in combination with chemotherapy and 802 patients received chemotherapy alone. Detailed safety data collection was primarily limited to Grade 3 and 4 adverse events and serious adverse events.

The population varied from 18–92 years of age and 56% were male; racial distribution was collected only for Study 6 (see **CLINICAL STUDIES** section) where 90% of patients were Caucasian, 5% were Black, 3% were Hispanic and 2% were from other racial groups. Patients received 4–8 doses of Rituxan at 375 mg/m².

The following adverse events, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 45%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). In one of these studies (Study 7), more detailed assessment of cardiac toxicity revealed that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders, with 4.5% vs. 1.0% incidences for R-CHOP and CHOP, respectively.

The following Grade 3 or 4 adverse events were reported more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other severe adverse events reported more commonly among patients receiving R-CHOP in one or more studies were viral infection, neutropenia and anemia.

Adverse Reactions in Patients with Rheumatoid Arthritis

In general, the adverse events observed in patients with RA were similar in type to those seen in patients with non-Hodgkin's lymphoma (see **WARNINGS**, **PRECAUTIONS** and other sections under **ADVERSE REACTIONS**). Specific safety considerations in this indication are discussed below.

Where specific percentages are noted, these data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 x 1000 mg) or placebo administered in combination with methotrexate.

Table 8
Incidence of All Adverse Events* Occurring in ≥2% and at Least 1% Greater than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N=393 n (%)	Rituxan + MTX N=540 n (%)
Abdominal Pain Upper	4 (1)	11 (2)
Anxiety	5 (1)	9 (2)
Arthralgia	14 (4)	31 (6)
Asthenia	1 (<1)	9 (2)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Hypercholesterolemia	1 (<1)	9 (2)
Hypertension	21 (5)	43 (8)
Migraine	2 (<1)	9 (2)
Nausea	19 (5)	41 (8)
Paresthesia	3 (<1)	12 (2)
Pruritus	5 (1)	26 (5)
Pyrexia	8 (2)	27 (5)
Rhinitis	6 (2)	14 (3)
Throat Irritation	0 (0)	11 (2)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Urticaria	3 (<1)	12 (2)

*Coded using MedDRA.

Infusion Reactions

In Rituxan RA placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse event during or within 24-hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse events during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing or interruption of the infusion) in 10% and 2% of patients receiving Rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of IV glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

Infections

In RA clinical studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis. The only infections to show an absolute increase over placebo of at least 1% were upper respiratory tract infections, which affected 7% of Rituxan-treated patients and 6% of placebo-treated patients and rhinitis, which affected 3% of Rituxan-treated patients and 2% of placebo-treated patients.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group. One fatal infection (bronchopneumonia) occurred with Rituximab monotherapy during the 24-week placebo-controlled period in one of the Phase 2 RA studies.

Cardiac Events

The incidence of serious cardiovascular events in the double-blind part of the clinical trials was 1.7% and 1.3% in Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all Rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

Immunogenicity

A total of 54/990 patients (5%) with RA tested positive for HACA. Of these, most became positive by week 24. Following the first course, however, some became positive at week 16 or after 24 weeks. Some patients tested positive after the second course of treatment. Limited data are available on the safety or efficacy of Rituxan retreatment in patients who develop HACA. One of 10 HACA-positive patients who received retreatment with Rituxan experienced a serious acute infusion reaction (bronchospasm). The clinical relevance of HACA formation in Rituximab-treated patients is unclear.

Post-Marketing Reports

The following adverse reactions have been identified during post-approval use of Rituxan in hematologic malignancies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituxan.

Hematologic: prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia.

Cardiac: fatal cardiac failure.

Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash.

Infection: increased in fatal infections in HIV-associated lymphoma.

Skin: severe mucocutaneous reactions.

Gastrointestinal: bowel obstruction and perforation.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m² have been given in dose-escalation clinical trials.[a]

DOSAGE AND ADMINISTRATION

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell Non-Hodgkin's Lymphoma

The recommended dose of Rituxan is 375 mg/m² IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy

The recommended dose of Rituxan is 375 mg/m² IV infusion once weekly for 4 doses in responding patients who develop progressive disease after previous Rituxan therapy. Currently there are limited data concerning more than 2 courses.

Previously Untreated, Follicular, CD20-Positive, B-Cell NHL

The recommended dose of Rituxan is 375 mg/m² IV infusion, given on Day 1 of each cycle of CVP chemotherapy, for up to 8 doses.

Previously Untreated, Low-Grade, CD20-Positive, B-Cell NHL

The recommended dose of Rituxan in patients who have not progressed following 6–8 cycles of CVP chemotherapy is 375 mg/m² IV infusion, once weekly for 4 doses every 6 months for up to 16 doses.

Diffuse Large B-Cell NHL

The recommended dose of Rituxan is 375 mg/m² IV per infusion given on Day 1 of each cycle of chemotherapy for up to 8 infusions.

Rheumatoid Arthritis

Rituxan is given as two-1000 mg IV infusions separated by 2 weeks. Glucocorticoids administered as methylprednisolone 100 mg IV or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions. Safety and efficacy of retreatment have not been established in controlled trials (see **PRECAUTIONS: Retreatment in patients with RA**).

Rituxan is given in combination with methotrexate.

Rituxan as a Component of Zevalin® (Ibritumomab Tiuxetan) Therapeutic Regimen

As a required component of the Zevalin therapeutic regimen, Rituxan 250 mg/m² should be infused within 4 hours prior to the administration of Indium-111- (In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin. Administration of Rituxan and In-111-Zevalin should precede Rituxan and Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

Rituxan may be administered in an outpatient setting. DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See *Administration*).

Instructions for Administration

Preparation for Administration

Use appropriate aseptic technique. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Infusion reactions may occur (see **BOXED WARNINGS**, **WARNINGS**, and **ADVERSE REACTIONS**). Premedication consisting of acetaminophen and an antihistamine should be considered before each infusion of Rituxan. Premedication may attenuate infusion reactions. Since transient hypotension may occur during Rituxan infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to Rituxan infusion.

First Infusion

The Rituxan solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. Rituxan should not be mixed or diluted with other drugs. If infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see **BOXED WARNINGS** and **WARNINGS**). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions

If the patient tolerated the first infusion well, subsequent Rituxan infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage

Rituxan vials are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or

shake. Refer to the "Preparation for Administration" section for information on the stability and storage of solutions of Rituxan diluted for infusion.

HOW SUPPLIED

Rituxan® (Rituximab) is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of Rituxan (10 mg/mL).

NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of Rituxan (10 mg/mL).

NDC 50242-053-06

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Rituxan® (Rituximab)

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7141414 LJ1240
Initial US Approval November 26, 1997
4835500
Revision Date September 29, 2006

Patient Information
Rituxan® (ri-tuk'-san)
(Rituximab)

Read this patient information leaflet when you have been prescribed Rituxan and each time you are scheduled to receive a Rituxan infusion. This information does not take the place of talking to your doctor about your medical condition or your treatment. Talk with your doctor if you have any questions about your treatment with Rituxan.

What is the most important safety information I should know about Rituxan?

Rituxan can cause the following serious side effects, some of which could be life-threatening:

- **Infusion reactions.** Tell your doctor or get medical treatment right away if you get hives, swelling, dizziness, blurred vision, drowsiness, headache, cough, wheezing, or have trouble breathing while receiving or after receiving Rituxan.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of certain blood cancers. TLS can cause kidney failure and the need for dialysis treatment. Patients receiving Rituxan for non-Hodgkin's lymphoma may get TLS.
- **Severe skin reactions.** Tell your doctor or get medical treatment right away if you get painful sores, ulcers, blisters, or peeling skin while receiving or after receiving Rituxan.

Also, see "What are possible side-effects with Rituxan?" for other serious side effects, some of which could be life-threatening.

What is Rituxan?

Rituxan is a biologic medicine used in adults:

- alone or with other anti-cancer medicines to treat certain types of non-Hodgkin's lymphoma (NHL).
- with another medicine called methotrexate to reduce the signs and symptoms of Rheumatoid Arthritis (RA) after at least one other medicine called a tumor necrosis factor (TNF) inhibitor has been used and did not work well.

Rituxan has not been studied in children.

How does Rituxan work?

Rituxan works by getting rid of certain B-cells in the blood. B-cells are a type of white blood cell found in the blood. B-cells usually help the body fight infection. B-cells play an important role in diseases such as NHL and RA. Rituxan may also get rid of healthy B-cells and this can give you a higher chance for getting infections.

Who should not receive Rituxan?

Do not receive Rituxan if you ever had an allergic reaction to Rituxan.

What should I tell my doctor before treatment with Rituxan?

Tell your doctor about all of your medical conditions, including if you:

- have an infection or have an infection that will not go away or that keeps coming back.
- are scheduled to have surgery.
- have had hepatitis B virus infection or are a carrier of hepatitis B virus. Your doctor should check you closely for signs of a hepatitis infection during treatment with Rituxan and for several months after treatment ends.
- have any scheduled vaccinations. It is not known if Rituxan affects your ability to respond to vaccines.
- have heart or lung problems.
- are pregnant or planning to become pregnant. It is not known if Rituxan can harm your unborn baby.
- are breastfeeding. It is not known if Rituxan passes into human breast milk. You should not breastfeed while being treated with Rituxan.

Tell your doctor about all the other medicines you take, including prescription and nonprescription medicines, vitamins, or herbal supplements. If you have RA, tell your doctor if you are taking or took another biologic medicine called a TNF inhibitor or a DMARD (disease modifying anti-rheumatic drug).

How do I receive Rituxan?

- Rituxan is given through a needle placed in a vein (IV infusion), in your arm. Rituxan therapy is given in different ways for NHL and RA. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe other medicines before each infusion of Rituxan to prevent or reduce pain, or to reduce fever and allergic reactions.
- Your doctor should do regular blood tests to check for side effects or reactions to Rituxan.

What are possible side effects with Rituxan?

Rituxan can cause the following serious side effects, some of which could be life-threatening side effects, including (See "What is the most important safety information I should know about Rituxan?")

- Infusion reactions
- Tumor Lysis Syndrome (TLS)
- Severe skin reactions

Other serious side effects with Rituxan include:

- **Hepatitis B virus reactivation.** Tell your doctor if you had Hepatitis B virus or are a carrier of Hepatitis B virus. Rituxan may make you sick with Hepatitis B virus again and cause serious liver problems. People with active liver disease due to Hepatitis B should stop receiving Rituxan.
- **Heart Problems.** Tell your doctor about any heart problems you have including chest pain (angina) and irregular heart beats. Rituxan can cause chest pain and irregular heart beats which may require treatment.
- **Infections.** Rituxan can increase your chances for getting infections. Call your doctor right away if you have a persistent cough, fever, chills, congestion, or any flu-like symptoms while receiving Rituxan. These symptoms may be signs of a serious infection.
- **Stomach and bowel problems.** Serious stomach and bowel problems have been seen when Rituxan has been used with anti-cancer medicines in some patients with non-Hodgkin's lymphoma. Call your doctor right away if you have any stomach area pain during treatment with Rituxan.

Common side effects with Rituxan include:

Fever, chills, shakes, itching, hives, sneezing, swelling, throat irritation or tightness, and cough. These usually occur within 24 hours after the first infusion. Other common side effects include headache, nausea, upper respiratory tract infection, and aching joints. If you have any of these symptoms, tell your doctor or nurse.

What if I still have questions?

If you have any questions about Rituxan or your health, talk with your doctor. You can also visit the Rituxan Internet sites at www.Rituxan.com or the companies' Internet sites at www.Gene.com or www.Biogenidec.com or call 1-877-4-Rituxan (877-474-8892).

Jointly Marketed by: Biogen Idec Inc. and Genentech, Inc.

Manufactured by:
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Assistant Commissioner for Patents
Box Provisional Application
Washington, D. C. 20231

Atty Dkt No. 018733/0931

Sir:

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT UNDER 37 CFR 1.53(c).**

INVENTORS/APPLICANTS:			
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (City & either State or Country)
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TITLE OF THE INVENTION
IMMUNOTHERAPY OF AUTOIMMUNE DISORDERS USING ANTI-CD22 ANTIBODIES

In connection with this application, the following are enclosed:

20 Pages of Specification (including 11 Claims)

-0- Sheets of Drawings

___Statement of Small Entity Status

The fee has been calculated as shown below. (Small entity fees indicated in parentheses.)

Filing Fee	$150 ($75)	$150.00
Rule 17(k) fee for non-English text	$130	
Assignment Recording Fee	$ 40	
	TOTAL FEE	$150.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No ☐ Yes, the name of the U.S. Government agency and the Government contract number are: .

A check in the amount of the above TOTAL FEE is attached. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 19-0741.

Respectfully submitted,

Date June 9, 1999

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IMMUNOTHERAPY OF AUTOIMMUNE DISORDERS USING ANTI-CD22 ANTIBODIES

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to immunotherapeutic methods for treating autoimmune disorders. In particular, this invention is directed to methods for treating autoimmune disorders by administering comparatively low doses of an entire antibody that binds to the CD22. The present invention also is directed to multimodal therapeutic methods in which the anti-CD22 administration is supplemented by administration of other therapeutic modalities.

Background

Antibodies against the CD20 antigen have been investigated for the therapy of B-cell lymphomas. For example, a chimeric anti-CD20 antibody, designated as "IDEC-C2B8," has activity against B-cell lymphomas when provided as unconjugated antibodies at repeated injections of doses exceeding 500 mg per injection. Maloney *et al., Blood 84*:2457 (1994); Longo, *Curr. Opin. Oncol. 8*:353 (1996). About 50 percent of non-Hodgkin's patients, having the low-grade indolent form, treated with this regimen showed responses. Therapeutic responses have also been obtained using ^{131}I-labeled B1 anti-CD-20 murine monoclonal antibody when provided as repeated doses exceeding 600 mg per injection. Kaminski *et al., N. Engl. J. Med. 329*:459 (1993); Press *et al., N. Engl. J. Med. 329*:1219 (1993); Press *et al., Lancet 346*:336 (1995). However, these antibodies, whether provided as unconjugated forms or radiolabeled forms, have not shown objective responses in patients with the more prevalent and lethal form of B-cell lymphoma, the intermediate or aggressive type.

Autoimmune diseases are a class of diseases associated with a B-cell disorder. Examples include immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, myasthenia gravis, lupus nephritis, lupus erythematosus, and rheumatoid arthritis. The most common treatments are corticosteroids and cytotoxic drugs, which can be very toxic. These drugs also suppress the entire immune system, can result in serious infection, and have adverse affects on the liver and kidneys. Other therapeutics that have been used to treat Class III autoimmune diseases to date have been directed against T-cells and macrophages. A need for more effective methods of treating autoimmune diseases, particularly Class III autoimmune diseases.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a method for treating autoimmune diseases using a comparatively low dose of a naked anti-CD22 antibody.

It is a further object of this invention to provide multimodal methods for treatment of autoimmune diseases in which a low dose of naked anti-CD22 antibody is supplemented with the administration of other therapeutic modalities, such as those directed against T-cells and macrophages.

These and other objects are achieved, in accordance with one embodiment of the present invention, by the provision of a method of treating an autoimmune disease, comprising the step of administering to a subject having an autoimmune disease a naked anti-CD22 antibody and a pharmaceutically acceptable carrier.

Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION

1. Overview

B-cell clones that bear autoantibody Ig-receptors are present in normal individuals. Autoimmunity results when these B-cells become overactive, and mature to plasma cells (in tissue) that secrete autoantibody. In accordance with the present invention, naked anti-CD22 antibodies are used to treat patients with autoimmune disorders by targeting B-cells.

2. Definitions

In the description that follows, and in documents incorporated by reference, a number of terms are used extensively. The following definitions are provided to facilitate understanding of the invention.

A structural gene is a DNA sequence that is transcribed into messenger RNA (mRNA) which is then translated into a sequence of amino acids characteristic of a specific polypeptide.

A promoter is a DNA sequence that directs the transcription of a structural gene. Typically, a promoter is located in the 5′ region of a gene, proximal to the transcriptional start site of a structural gene. If a promoter is an inducible promoter, then the rate of transcription increases in response to an inducing agent. In contrast, the rate of transcription is not regulated by an inducing agent when the promoter is a constitutive promoter.

An isolated DNA molecule is a fragment of DNA that is not integrated in the genomic DNA of an organism. For example, a cloned antibody gene is a DNA fragment that has been separated from the genomic DNA of a mammalian cell. Another example of an isolated DNA molecule is a chemically synthesized DNA molecule that is not integrated in the genomic DNA of an organism.

An enhancer is a DNA regulatory element that can increase the efficiency of transcription, regardless of the distance or orientation of the enhancer relative to the start site of transcription.

Complementary DNA (cDNA) is a single-stranded DNA molecule that is formed from a mRNA template by the enzyme reverse transcriptase. Typically, a primer complementary to portions of mRNA is employed for the initiation of reverse transcription. Those skilled in the art also use the term "cDNA" to refer to a double-stranded DNA molecule consisting of such a single-stranded DNA molecule and its complementary DNA strand.

The term expression refers to the biosynthesis of a gene product. For example, in the case of a structural gene, expression involves transcription of the structural gene into mRNA and the translation of mRNA into one or more polypeptides.

A cloning vector is a DNA molecule, such as a plasmid, cosmid, or bacteriophage that has the capability of replicating autonomously in a host cell. Cloning vectors typically contain one or a small number of restriction endonuclease recognition sites at which foreign DNA sequences can be inserted in a determinable fashion without loss of an essential biological function of the vector, as well as a marker gene that is suitable for use in the identification and selection of cells transformed with the cloning vector. Marker genes typically include genes that provide tetracycline resistance or ampicillin resistance.

An expression vector is a DNA molecule comprising a gene that is expressed in a host cell. Typically, gene expression is placed under the control of certain regulatory elements, including constitutive or inducible promoters, tissue-specific regulatory elements, and enhancers. Such a gene is said to be "operably linked to" the regulatory elements.

A recombinant host may be any prokaryotic or eukaryotic cell that contains either a cloning vector or expression vector. This term also includes those prokaryotic or eukaryotic cells that have been genetically engineered to contain the cloned gene(s) in the chromosome or genome of the host cell.

A chimeric antibody is a recombinant protein that contains the variable domains and complementary determining regions derived from a rodent antibody, while the remainder of the antibody molecule is derived from a human antibody.

Humanized antibodies are recombinant proteins in which murine complementarity determining regions of a monoclonal antibody have been

transferred from heavy and light variable chains of the murine immunoglobulin into a human variable domain.

Human antibodies are antibodies that either are isolated from humans and then grown out in culture or are made using animals whose immune systems have been altered so that they respond to antigen stimulation by producing human antibodies.

As used herein, a therapeutic agent is a molecule or atom, which is conjugated to an antibody moiety to produce a conjugate which is useful for therapy. Examples of therapeutic agents include drugs, toxins, immunomodulators, boron compounds and radioisotopes.

A naked antibody is an entire antibody which is not conjugated with a therapeutic agent. Naked antibodies include both polyclonal and monoclonal antibodies, as well as certain recombinant antibodies, such as chimeric and humanized antibodies.

3. Production of Anti-CD22 Monoclonal Antibodies, Humanized Antibodies, Primate Antibodies and Human Antibodies

Anti-CD20 antibodies are known generally to those of skill in the art. See, for example, Ghetie *et al., Cancer Res. 48*:2610 (1988); Hekman *et al., Cancer Immunol. Immunother. 32*:364 (1991); Kaminski *et al., N. Engl. J. Med. 329*:459 (1993); Press *et al., N. Engl. J. Med. 329*:1219 (1993); Maloney *et al., Blood 84*:2457 (1994); Press *et al., Lancet 346*:336 (1995); Longo, *Curr. Opin. Oncol. 8*:353 (1996). More particularly, rodent monoclonal antibodies to CD22 can be obtained by methods known to those skilled in the art. See generally, for example, Kohler and Milstein, *Nature 256*:495 (1975), and Coligan *et al.* (eds.), CURRENT PROTOCOLS IN IMMUNOLOGY, VOL. 1, pages 2.5.1-2.6.7 (John Wiley & Sons 1991) ["Coligan"]. Briefly, monoclonal antibodies can be obtained by injecting mice with a composition comprising CD22, verifying the presence of antibody production by removing a serum sample, removing the spleen to obtain B-lymphocytes, fusing the B-lymphocytes with myeloma cells to produce hybridomas, cloning the hybridomas, selecting positive clones which produce anti-CD22

antibodies, culturing the clones that produce antibodies to the antigen, and isolating the antibodies from the hybridoma cultures.

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, for example, Coligan at pages 2.7.1-2.7.12 and pages 2.9.1-2.9.3. Also, see Baines *et al.*, "Purification of Immunoglobulin G (IgG)," in METHODS IN MOLECULAR BIOLOGY, VOL. 10, pages 79-104 (The Humana Press, Inc. 1992).

Suitable amounts of the well-characterized CD22 antigen for production of antibodies can be obtained using standard techniques. As an example, CD22 can be immunoprecipitated from B-lymphocyte protein using the deposited antibodies described by Tedder *et al.*, U.S. patent No. 5,484,892 (1996).

Alternatively, CD22 protein can be obtained from transfected cultured cells that overproduce CD22. Expression vectors that comprise DNA molecules encoding CD22 protein can be constructed using published CD22 nucleotide sequences. See, for example, Wilson *et al.*, *J. Exp. Med. 173*:137 (1991); Wilson *et al.*, *J. Immunol. 150*:5013 (1993). As an illustration, DNA molecules encoding CD22 can be obtained by synthesizing DNA molecules using mutually priming long oligonucleotides. See, for example, Ausubel *et al.*, (eds.), CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, pages 8.2.8 to 8.2.13 (1990) ["Ausubel"]. Also, see Wosnick *et al.*, *Gene 60*:115 (1987); and Ausubel *et al.* (eds.), SHORT PROTOCOLS IN MOLECULAR BIOLOGY, 3rd Edition, pages 8-8 to 8-9 (John Wiley & Sons, Inc. 1995). Established techniques using the polymerase chain reaction provide the ability to synthesize genes as large as 1.8 kilobases in length. Adang *et al.*, *Plant Molec. Biol. 21*:1131 (1993); Bambot *et al.*, *PCR Methods and Applications 2*:266 (1993); Dillon *et al.*, "Use of the Polymerase Chain Reaction for the Rapid Construction of Synthetic Genes," in METHODS IN MOLECULAR BIOLOGY, Vol. 15: PCR PROTOCOLS: CURRENT METHODS AND APPLICATIONS, White (ed.), pages 263-268, (Humana Press, Inc. 1993).

In a variation of this approach, anti-CD22 monoclonal antibody can be obtained by fusing myeloma cells with spleen cells from mice immunized with a murine pre-B cell line stably transfected with CD22 cDNA. See Tedder *et al.*, U.S. patent No. 5,484,892 (1996).

One example of a suitable murine anti-CD22 monoclonal antibody is the LL2 (formerly EPB-2) monoclonal antibody, which was produced against human Raji cells derived from a Burkitt lymphoma. Pawlak-Byczkowska *et al.*, *Cancer Res.* *49*:4568 (1989). This monoclonal antibody has an IgG_{2a} isotype, and the antibody is rapidly internalized into lymphoma cells. Shih *et al*, *Int. J. Cancer* *56*:538 (1994). Immunostaining and *in vivo* radioimmunodetection studies have demonstrated the excellent sensitivity of LL2 in detecting B-cell lymphomas. Pawlak-Byczkowska *et al.*, *Cancer Res.* *49*:4568 (1989); Murthy *et al.*, *Eur. J. Nucl. Med.* *19*:394 (1992). Moreover, ^{99m}Tc-labeled LL2-Fab' fragments have been shown to be useful in following upstaging of B-cell lymphomas, while ^{131}I-labeled intact LL2 and labeled LL2 $F(ab')_2$ fragments have been used to target lymphoma sites and to induce therapeutic responses. Murthy *et al.*, *Eur. J. Nucl. Med.* *19*:394 (1992); Mills *et al.*, *Proc. Am. Assoc. Cancer Res.* *34*:479 (1993) [Abstract 2857]; Baum *et al.*, *Cancer 73 (Suppl. 3)*:896 (1994); Goldenberg *et al.*, *J. Clin. Oncol.* *9*:548 (1991). Furthermore, Fab' LL2 fragments conjugated with a derivative of *Pseudomonas* exotoxin has been shown to induce complete remissions for measurable human lymphoma xenografts growing in nude mice. Kreitman *et al.*, *Cancer Res.* *53*:819 (1993).

In an additional embodiment, an antibody of the present invention is a chimeric antibody in which the variable regions of a human antibody have been replaced by the variable regions of a rodent anti-CD22 antibody. The advantages of chimeric antibodies include decreased immunogenicity and increased *in vivo* stability.

Techniques for constructing chimeric antibodies are well known to those of skill in the art. As an example, Leung *et al.*, *Hybridoma* *13*:469 (1994), describe how they produced an LL2 chimera by combining DNA sequences encoding the V_κ and V_H domains of LL2 monoclonal antibody with respective human κ and IgG_1

constant region domains. This publication also provides the nucleotide sequences of the LL2 light and heavy chain variable regions, V_κ and V_H, respectively.

In another embodiment, an antibody of the present invention is a subhuman primate antibody. General techniques for raising therapeutically useful antibodies in baboons may be found, for example, in Goldenberg *et al.*, international patent publication No. WO 91/11465 (1991), and in Losman *et al., Int. J. Cancer 46*: 310 (1990).

In yet another embodiment, an antibody of the present invention is a "humanized" monoclonal antibody. That is, mouse complementarity determining regions are transferred from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, followed by the replacement of some human residues in the framework regions of their murine counterparts. Humanized monoclonal antibodies in accordance with this invention are suitable for use in therapeutic methods. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi *et al., Proc. Nat'l Acad. Sci. USA 86*: 3833 (1989). Techniques for producing humanized monoclonal antibodies are described, for example, by Jones *et al., Nature 321*:522 (1986), Riechmann *et al., Nature 332*:323 (1988), Verhoeyen *et al., Science 239*:1534 (1988), Carter *et al., Proc. Nat'l Acad. Sci. USA 89*:4285 (1992), Sandhu, *Crit. Rev. Biotech. 12*:437 (1992), and Singer *et al., J. Immun. 150*:2844 (1993). The publication of Leung *et al., Mol. Immunol. 32*:1413 (1995), describes the construction of humanized LL2 antibody.

In another embodiment, an antibody of the present invention is a human monoclonal antibody. Such antibodies are obtained from transgenic mice that have been "engineered" to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described by Green *et al.*,

Nature Genet. 7:13 (1994), Lonberg *et al.*, *Nature* 368:856 (1994), and Taylor *et al.*, *Int. Immun.* 6:579 (1994).

4. Coupling of Antibodies to Lipid Emulsions

Long-circulating sub-micron lipid emulsions, stabilized with poly(ethylene glycol)-modified phosphatidylethanolamine (PEG-PE), can be used as drug carriers for the anti-CD22 antibodies of the present invention. The emulsions are composed of two major parts: an oil core, *e.g.*, triglyceride, stabilized by emulsifiers, *e.g.*, phospholipids. The poor emulsifying properties of phospholipids can be enhanced by adding a biocompatible co-emulsifier such as polysorbate 80. In a preferred embodiment, the anti-CD22 antibody is conjugated to the surface of the lipid emulsion globules with a poly(ethylene glycol)-based, heterobifunctional coupling agent, poly(ethylene glycol)-vinylsulfone-N-hydroxy-succinimidyl ester (NHS-PEG-VS).

The submicron lipid emulsion is prepared and characterized as described. Lundberg, *J. Pharm. Sci.*, 83:72 (1993); Lundberg *et al.*, *Int. J. Pharm.*, 134:119 (1996). The basic composition of the lipid emulsion is triolein:DPPC:polysorbate 80, 2:1:0.4 (w/w). When indicated, PEG-DPPE is added into the lipid mixture at an amount of 2-8 mol% calculated on DPPC.

The coupling procedure starts with the reaction of the NHS ester group of NHS-PEG-VS with the amino group of distearoyl phosphatidyl-ethanolamine (DSPE). Twenty-five μmol of NHS-PEG-VS are reacted with 23 μmol of DSPE and 50 μmol triethylamine in 1 ml of chloroform for 6 hours at 40°C to produce a poly(ethylene glycol) derivative of phosphatidyl-ethanolamine with a vinylsulfone group at the distal terminus of the poly(ethylene glycol) chain (DSPE-PEG-VS). For antibody conjugation, DSPE-PEG-VS is included in the lipid emulsion at 2 mol% of DPPC. The components are dispersed into vials from stock solutions at -20°C, the solvent is evaporated to dryness under reduced pressure. Phosphate-buffered saline (PBS) is added, the mixture is heated to 50°C, vortexed for 30 seconds and sonicated with a MSE probe sonicator for 1 minute. Emulsions can be stored at 4°C, and preferably are used for conjugation within 24 hours.

Coupling of anti-CD22 antibodies to emulsion globules is performed via a reaction between the vinylsulfone group at the distal PEG terminus on the surface of the globules and free thiol groups on the antibody. Vinylsulfone is an attractive derivative for selective coupling to thiol groups. At approximately neutral pH, VS will couple with a half life of 15-20 minutes to proteins containing thiol groups. The reactivity of VS is slightly less than that of maleimide, but the VS group is more stable in water and a stable linkage is produced from reaction with thiol groups.

Before conjugation, the antibody is reduced by 50 mM 2-mercaptoethanol for 10 minntes at 4°C in 0.2 M Tris buffer (pH 8.7). The reduced antibody is separated from excess 2-mercaptoethanol with a Sephadex G-25 spin column, equilibrated in 50 mM sodium acetate buffered 0.9% saline (pH 5.3). The product is assayed for protein concentration by measuring its absorbance at 280 nm (and assuming that a 1 mg/ml antibody solution of 1.4) or by quantitation of ^{125}I-labeled antibody. Thiol groups are determined with Aldrithiol™ following the change in absorbance at 343 nm and with cystein as standard.

The coupling reaction is performed in HEPES-buffered saline (pH 7.4) overnight at ambient temperature under argon. Excess vinylsulfone groups are quenched with 2 mM 2-mercaptoethanol for 30 minutes, excess 2-mercaptoethanol and antibody are removed by gel chromatography on a Sepharose CL-48 column. The immunoconjugates are collected near the void volume of the column, sterilized by passage through a 0.45 μm sterile filter, and stored at 4°C.

Coupling efficiency is calculated using ^{125}I-labeled antibody. Recovery of emulsions is estimated from measurements of [^{14}C]DPPC in parallel experiments. The conjugation of reduced LL2 to the VS group of surface-grafted DSPE-PEG-VS is very reproducible with a typical efficiency of near 85%.

5. Therapeutic Use of Anti-CD22 Antibodies in Simple and Multimodal Regimens

The present invention contemplates the use of naked anti-CD22 antibodies as the primary therapeutic composition for treatment of autoimmune diseases. Such

a composition can contain polyclonal anti-CD22 antibodies or monoclonal anti-CD22 antibodies. Preferred antibodies are LL2 antibodies, including murine LL2 monoclonal antibody, chimeric LL2 antibody, and humanized LL2 antibody.

In addition, a therapeutic composition of the present invention can contain a mixture of monoclonal naked anti-CD22 antibodies directed to different, non-blocking CD22 epitopes. Monoclonal antibody cross-inhibition studies have identified five epitopes on CD22, designated as epitopes A-E. See, for example, Schwartz-Albiez *et al.*, "The Carbohydrate Moiety of the CD22 Antigen Can Be Modulated by Inhibitors of the Glycosylation Pathway," in LEUKOCYTE TYPING IV. WHITE CELL DIFFERENTIATION ANTIGENS, Knapp *et al.* (eds.), p. 65 (Oxford University Press 1989). As an illustration, the LL2 antibody binds with epitope B. Stein *et al., Cancer Immunol. Immunother.* 37:293 (1993). Accordingly, the present invention contemplates therapeutic compositions comprising a mixture of monoclonal anti-CD22 antibodies that bind at least two CD22 epitopes. For example, such a mixture can contain monoclonal antibodies that bind with at least two CD22 epitopes selected from the group consisting of epitope A, epitope B, epitope C, epitope D and epitope E.

Methods for determining the binding specificity of an anti-CD22 antibody are well-known to those of skill in the art. General methods are provided, for example, by Mole, "Epitope Mapping," in METHODS IN MOLECULAR BIOLOGY, VOLUME 10: IMMUNOCHEMICAL PROTOCOLS, Manson (ed.), pages 105-116 (The Humana Press, Inc. 1992). More specifically, competitive blocking assays to determine CD22 epitope specificity are described by Stein *et al.*, *Cancer Immunol. Immunother.* 37:293 (1993), and by Tedder *et al.*, U.S. patent No. 5,484,892 (1996).

The Tedder patent also describes the production of CD22 mutants, which lack one or more immunoglobulin-like domains. These mutant proteins were used to determine that immunoglobulin-like domains 1, 2, 3, and 4 correspond with epitopes A, D, B, and C, respectively. Thus, binding a test antibody with a panel of CD22 proteins lacking particular immunoglobulin-like domain can also identify CD22 epitope specificity.

Although naked anti-CD22 antibodies are the primary therapeutic compositions for treatment of autoimmune diseases, the efficacy of such antibody therapy can be enhanced by supplementing the naked antibodies, with supplemental therapies described herein. In such multimodal regimens, the supplemental therapeutic compositions can be administered before, concurrently or after administration of the anti-CD22 antibodies. The therapeutic compositions described herein are useful for treatment of autoimmune diseases, particularly for the treatment of Class III autoimmune diseases including immune-mediated thrombocytopenias, such as acute idiopathic thrombocytopenic purpura and chronic idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, Henoch-Schonlein purpura, post-streptococcal nephritis, erythema nodosum, Takayasu's arteritis, Addison's disease, rheumatoid arthritis multiple sclerosis, sarcoidosis, ulcerative colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitis ubiterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, pamphigus vulgaris, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis and fibrosing alveolitis. In this context, the therapeutic compositions are used to deplete the blood of normal B-cells for an extended period.

Multimodal therapy of Class III autoimmune diseases further may comprise co-administration of therapeutics that are targeted against T-cells or macrophages, such as antibodies directed against T-cell epitopes, more particularly against the CD4 and CD5 epitopes. Gamma globulins also may be co-administered. In some cases, it may be desirable to co-administer corticosteroids and possibly also cytotoxic drugs. In this case, lower doses of the corticosteroids and cytotoxic drugs can be used as compared to the doses used in conventional therapies, thereby reducing the negative side effects of these therapeutics. The supplemental

therapeutic compositions can be administered before, concurrently or after administration of the naked anti-CD22.

In general, the dosage of administered anti-CD22 antibodies will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition and previous medical history. Typically, it is desirable to provide the recipient with a dosage of antibody component, immunoconjugate or fusion protein which is in the range of from about 1 pg/kg to 10 mg/kg (amount of agent/body weight of patient), although a lower or higher dosage also may be administered as circumstances dictate.

Administration of antibodies to a patient can be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, by perfusion through a regional catheter, or by direct intralesional injection. When administering therapeutic proteins by injection, the administration may be by continuous infusion or by single or multiple boluses. Intravenous injection provides a useful mode of administration due to the thoroughness of the circulation in rapidly distributing antibodies.

Preferably, naked anti-CD22 antibodies are administered at low protein doses, such as 20 to 1200 milligrams protein per dose, given once, or repeatedly, parenterally. Alternatively, naked anti-CD22 antibodies are administered in doses of 20 to 1000 milligrams protein per dose, or 20 to 500 milligrams protein per dose, or 20 to 100 milligrams protein per dose.

The anti-CD22 antibodies, alone or conjugated to liposomes, can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic proteins are combined in a mixture with a pharmaceutically acceptable carrier. A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known to those in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, 19th Ed. (1995).

For purposes of therapy, naked antibodies are administered to a patient in a therapeutically effective amount in a pharmaceutically acceptable carrier. In this

regard, a "therapeutically effective amount" is one that is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. In the present context, an agent is physiologically significant if its presence results in the inactivation or killing of targeted B-cells.

Additional pharmaceutical methods may be employed to control the duration of action of an antibody in a therapeutic application. Control release preparations can be prepared through the use of polymers to complex or adsorb the antibody. For example, biocompatible polymers include matrices of poly(ethylene-co-vinyl acetate) and matrices of a polyanhydride copolymer of a stearic acid dimer and sebacic acid. Sherwood *et al.*, *Bio/Technology* 10:1446 (1992). The rate of release of an antibody from such a matrix depends upon the molecular weight of the protein, the amount of antibody within the matrix, and the size of dispersed particles. Saltzman *et al.*, *Biophys. J.* 55:163 (1989); Sherwood *et al.*, *supra.* Other solid dosage forms are described in REMINGTON'S PHARMACEUTICAL SCIENCES, 19th ed. (1995).

The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

EXAMPLE 1:

Treatment of a patient with humanized LL2

A undergoes therapy with humanized LL2 monoclonal antibody. The patient was infused intravenously with 634 mg of humanized LL2 antibody, and the treatment was repeated 6, 13, and 20 days following this initial treatment. Immediately following the last dose, the serum value of hLL2 was 389.7 μg/ml, and one month following the last dose the serum value of hLL2 was 186.5 μg/ml. Normal B-cells in the blood prior to therapy with hLL2 were completely depleted from the blood 2 months post-therapy, and there was minimal reappearance of normal B cells five months post-therapy. The results are shown in the following table.

TABLE 1: B-cells and T-cells in blood

Day	T4/T8	% blood B-cells				% blood T-cells	% blood HLA-Dr (Ia)
		CD19	CD20	kappa	lambda	CD3	
		Flow cytometry					
0	1.5	5	5	6	2	38	6
28		hLL2 therapy					
34		hLL2 therapy					
41		hLL2 therapy					
48		hLL2 therapy					
		Flow cytometry					
76	1.3	<1	<1	<1	<1	71	6
191	2.0	1	1	<1	<1	73	4

EXAMPLE 2:

Treatment of a patient with chronic idiopathic thrombocytopenia purpura

A 50 year old female with chronic idiopathic thrombocytopenia purpura has been treated with prednisone, gamma globulins, and high dose dexamethason, but the disease progresses. She undergoes spleenectomy, which fails to stabilize the disease. Her platelet count falls to less than 100,000/microliter, and hemorrahgic events increase in frequency. The patient is then treated with hLL2, 600 mg intravenously each week, for a period of four weeks. Four weeks after the last dose of hLL2 a marked increase in platelet number is observed, and the hemorrahgic events become infrequent. Three months after the last antibody infusion the disease is in remission.

EXAMPLE 3:

Treatment of a patient with progressive rheumatoid arthritis

A 60 year old male, with severe progressive rheumatoid arthritis of the finger joints, wrists, and elbows, has failed therapy with methotrexate, and obtains only minor relief when placed on Enbrel therapy. The patient is then treated with hLL2, 700 mg intravenously each week, for a period of four weeks. After 3 months a 20% improvement in measures of disease activity is observed, which is maintained for 6 months. The patient is again treated with hLL2, at the same dose and frequency. The patient continues to improve, and 6 months after the second hLL2 therapy, a 50% improvement is observed. No human anti-hLL2 antibodies are observed at any time during, or after the hLL2 therapy. Although normal B-cells are depleted from the blood, no infectious complications, or other drug-related toxicity are observed.

EXAMPLE 4:

Treatment of a patient with myasthenia gravis

A 55 year old male has failed all conventional therapy for myasthenia gravis, and is admitted to a neurological intensive therapy unit. The patient was stabilized by plasma exchange, and given intravenous immunoglobulin to reduce the titer of antiacetylcholine receptor antibody. The patient remained bedridden, and was then treated with hLL2, 800 mg intravenously each week, for a period of four weeks. One week after the last dose of hLL2, no blood B-cells were detectable, and a significant drop in the titer of the anti-acetylcholine was observed. Two months after the last hLL2 dose the patient was mobile, and was released from the hospital.

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention, which is defined by the following claims.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those in the art to which the invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference in its entirety.

What Is Claimed Is:

1. A method for treating an autoimmune disorder, comprising the step of administering to a subject having an autoimmune disorder a therapeutic composition comprising a pharmaceutically acceptable carrier and at least one naked anti-CD22 antibody.

2. The method of claim 1, wherein said therapeutic composition is administered parenterally in a dosage of from 20 to 1200 mg per dose.

3. The method of claim 2, wherein said subject receives said anti-CD22 antibody in repeated parenteral dosages.

4. The method of claim 1, wherein said anti-CD22 antibody is selected from the group consisting of subhuman primate antibody, murine monoclonal antibody, chimeric antibody, and humanized antibody.

5. The method of claim 4, wherein said anti-CD22 antibody is the murine, chimeric, or humanized LL2 antibody.

6. The method of claim 1, wherein said therapeutic composition comprises at least two monoclonal antibodies that bind with distinct CD22 epitopes, wherein said CD22 epitopes are selected from the group consisting of epitope A, epitope B, epitope C, epitope D and epitope E.

7. The method of claim 1, wherein said autoimmune disease is selected from the group consisting acute idiopathic thrombocytopenic purpura, chronic idiopathic thrombocytopenic purpura, dermatomyositis, Sydenham's chorea, myasthenia gravis, systemic lupus erythematosus, lupus nephritis, rheumatic fever, polyglandular syndromes, bullous pemphigoid, diabetes mellitus, Henoch-Schonlein purpura, post-streptococcal nephritis, erythema nodosum, Takayasu's arteritis, Addison's disease, rheumatoid arthritis multiple sclerosis, sarcoidosis, ulcerative

colitis, erythema multiforme, IgA nephropathy, polyarteritis nodosa, ankylosing spondylitis, Goodpasture's syndrome, thromboangitis ubiterans, Sjogren's syndrome, primary biliary cirrhosis, Hashimoto's thyroiditis, thyrotoxicosis, scleroderma, chronic active hepatitis, polymyositis/dermatomyositis, polychondritis, pamphigus vulgaris, Wegener's granulomatosis, membranous nephropathy, amyotrophic lateral sclerosis, tabes dorsalis, giant cell arteritis/polymyalgia, pernicious anemia, rapidly progressive glomerulonephritis and fibrosing alveolitis.

8. The method of claim 1, further comprising the step of administering a secondary therapeutic directed against T-cells or macrophages.

9. The method of claim 8, wherein said secondary therapeutic is administered prior to the administration of said therapeutic composition.

10. The method of claim 9, wherein said secondary therapeutic is administered concurrently with the administration of said therapeutic composition.

11. The method of claim 10, wherein said secondary therapeutic is administered after the administration of said therapeutic composition.

ABSTRACT OF THE DISCLOSURE

Naked antibodies that bind with the CD22 antigen provide an effective means to treat autoimmune disorders. Immunotherapy with naked anti-CD22 antibodies requires comparatively low doses of antibody protein, and can be used effectively in multimodal therapies.